

# A niche mechanism for $\beta$ -cell regeneration in type 1 diabetes

Hodson, David

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# A Niche Mechanism for $\beta$ -Cell Regeneration in Type 1 Diabetes

David J. Hodson

Type 1 diabetes (T1D) occurs when insulin-secreting pancreatic  $\beta$ -cells are selectively destroyed by immune attack.<sup>[1]</sup> Treatment of T1D therefore requires insulin replacement therapy to enable control over blood glucose levels. While effective, there are issues with injecting insulin, including the loss of protective counter-regulatory responses. Replenishment of endogenous  $\beta$ -cells therefore remains a desirable goal for T1D therapy. However, because  $\beta$ -cell turnover in adults is largely through replication<sup>[2]</sup> and  $\beta$ -cells are lost during T1D, other non- $\beta$ -cell sources need to be identified.

Suggesting that progenitors might be important during islet injury,  $\beta$ -cells renew following diphtheria toxin-mediated ablation.<sup>[3]</sup> Remarkably, these  $\beta$ -cells descend from  $\alpha$ - and  $\delta$ -cells.<sup>[3]</sup> Given that  $\alpha$ -cells persist in T1D islets, this could provide a basis for the restoration of functional  $\beta$ -cell mass. Whether or not similar mechanisms influence  $\beta$ -cell renewal in the absence of manoeuvres to induce profound plasticity has been difficult to assess.

In this issue of BioEssays, Huising et al.<sup>[4]</sup> discuss and expand on recent findings suggesting that plasticity is intrinsic to the unstressed islet. Based on absence of the  $\beta$ -cell maturity marker, urocortin 3 (Ucn3), recent studies have shown the existence of a neogenic niche in adult islets.<sup>[5]</sup>  $\beta$ -cells belonging to the niche occupy the islet periphery, where  $\alpha$ -cells aggregate, and constitute just 1.5% of the total population. These “virgin” cells are insulin+, but are transcriptionally immature and glucose unresponsive. Notably, virgin  $\beta$ -cells were shown to represent an intermediate stage in the transdifferentiation of  $\alpha$ - to  $\beta$ -cells. These findings are important because they suggest that progenitor-like cells with an  $\alpha$ -cell ancestry might give rise to new  $\beta$ -cells.

So how do the authors propose to further test this intriguing hypothesis?  $\beta$ -cells can be labeled using reporter lines, before tracking and quantification. While identical experiments showed

that  $\beta$ -cell renewal is through replication,<sup>[2]</sup> the Cre-driver lines used display poor recombination efficiency, decreasing the power to detect changes. Lineage tracing can also be deployed to determine whether virgin  $\beta$ -cells convert into mature  $\beta$ -cells. To understand the contribution of transdifferentiation to this process, the number of mature (Ucn3+)  $\beta$ -cells with an  $\alpha$ -cell lineage label can be quantified. If the neogenic niche is relevant for T1D, the authors suggest that  $\beta$ -cells possessing an  $\alpha$ -cell lineage label should accumulate in the face of ongoing immune destruction in NOD mouse models.

The proposed studies will provide further mechanistic insight into the role of the neogenic niche in  $\beta$ -cell regeneration. However, lineage tracing has drawbacks. In particular, transgenic  $\alpha$ -cell driver lines can possess variable recombination efficiency and leakiness in different labs. Latest generation CRISPR knock-in animals should help here. It will be interesting to understand how the islet microenvironment influences the niche. This could take the form of experiments in re-aggregated islets where normal  $\alpha$ -/ $\beta$ -cell interactions are lost. Whether or not virgin  $\beta$ -cells give rise to mature  $\beta$ -cells that can proliferate in the face of immune infiltration also needs to be established. Perhaps the most difficult aspect of studying  $\beta$ -cell regeneration, however, is extending findings to humans. While Ucn3-negative  $\beta$ -cells also exist in islets from young donors, their capacity to form new  $\beta$ -cells is unknown. Isolation of these putative virgin  $\beta$ -cells for screening with compound libraries might help identify lead candidates with replicative/proliferative potential. Lastly, the extent to which virgin  $\beta$ -cells can replenish the  $\beta$ -cell complement needs to be established to better demonstrate clinical applicability.

## Conflict of Interest

The author declares no conflict of interest.

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Dr. D. J. Hodson  
Institute of Metabolism and Systems Research (IMSR)  
Centre of Membrane Proteins and Receptors (COMPARE)  
University of Birmingham  
Birmingham, UK  
E-mail: d.hodson@bham.ac.uk

Dr. D. J. Hodson  
Centre for Endocrinology, Diabetes and Metabolism  
Birmingham Health Partners  
Birmingham, UK

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